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PHOTODERMATITIS DUE TO TETRACHLORSALICYLANILIDE.

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THE summer of 1960 was not notable for its sunshine and cases of photodermatitis were uncommon, at any rate in Buckinghamshire. Two cases seen in September, however, drew attention to the problem of unexplained light sensitivity. Though these were not connected with the subsequent outbreak which is the subject of this paper, they stimulated an interest into possible causes, including airborne sensitizing pollens.

At the beginning of November there occurred the first of a series of 53 cases of acute photodermatitis. Twenty-four of these were seen in hospital and insurance practice in Buckinghamshire and 29 occurred in a factory in Maidenhead.

HOSPITAL CASES.

On 5 November, a 36-year-old garage worker came to the clinic complaining that his face and neck had become red and swollen ten days previously, after a trip to Oxford in an open car on a fine day. A relapse occurred a few days later, at the weekend. Patch-tests to oils and greases were negative. Provocative tests to sulphonomides, chlorpromazine and promethazine elicited no reaction. Two days later I was called urgently to see another patient at his home. This was a 73-year-old clerk of works who was out in the open air most of the day. Ten days previously he also had developed, quite suddenly, marked erythema and oedema of the face and neck. Shortly afterwards the backs of the hands were similarly affected. The distribution was striking and entirely confined to the light-exposed areas. Although he had been in hospital in 1954 with generalized seborrhoeic dermatitis, he had been free from this in recent years and the scalp and rest of the skin were entirely clear of eruption. Light-provoked patch-tests to *Solidago* (Golden Rod) were negative, as were provocative drug tests.

Six days later two further cases occurred in a brother and sister, a butler and domestic helper. The onset had occurred during the previous month and also started

with swelling and redness of the face. Two further cases, in a gardener and a sawyer, were seen in the next three weeks.

The fact that fowl-pest had been prevalent in the extensive local " broiler " industry led to enquiries about possible antibiotic or antiseptic agents that might either have been given to chickens or used as a preservative in pre-packed foods and sausages. (The eruption resembled the erythematous photodermatitis provoked by sulphonomides). But no likely substances had been used.

Factory Outbreak.

Early in January 1961, two men examined for the Ministry of Pensions and National Insurance, and one man referred to my clinic, gave an identical account of the onset of a rash similar to those already described. They all worked in the same factory and Dr. D. Wynn-Jones, the factory medical officer, kindly arranged for me to visit the factory and gave an account of 20 workers that had been so far affected (9 further cases occurred later making a total of 29 out of 106 at risk).

All those affected at that time—and all but three eventually—worked in a large " shop " where metal was treated at high temperature, but cases had occurred, some of them quite severe, in men far removed from the furnaces and in workers in the steel stores at the end of the shop. There was a possibility that the workers were liable to contact with aromatic hydrocarbons liberated from the " cracking " of the cooling oil as the very hot strip passed through it. Numerous samples were taken for testing. The washing facilities were excellent and it was noticed that there was a stack of bars of a popular germicidal toilet soap in the workroom. On further enquiry it was confirmed that this was the only " shop " in which this was used and that it was used in very considerable quantity (thirty bars a day) by the workers, whose occupation was dirty. It was also noted that the affected men usually reported on Mondays, having become worse at the weekends ; and that a change in pattern from an initial burning erythema to a more acute eczematous eruption took place in some men over Christmas (D. Wynn-Jones, 1961). Furthermore it was particularly noted that five severe recurrences occurred over the Christmas holidays when the men were away from work for five days. Patch tests on two affected men against dilutions of oils were negative, but it was noticed in the course of investigation that a solution of the toilet soap was fluorescent. A 1% solution of the soap was the only substance that gave a faint equivocal positive result on patch testing. The factory was advised to discontinue the use of this soap and did so immediately. A few new cases and some recurrences occurred at the end of January, but none was reported after 7 February, when one man had a severe recurrence after working in his garden on the previous Saturday. On subsequent visits to the factory it was found that many of the severely affected men used the same toilet soap at home—a much larger proportion of workers did this than in the general population.

Further Hospital Cases.

Meanwhile a review of the first six cases and of three new cases seen in the clinics revealed that all the patients had used the same soap for washing except one who used a less popular, but similar soap. Two of the new cases occurred in a man and wife ; she did not use the soap on her face and her hands only were affected ; her husband was severely affected and had to be admitted to hospital, the first of seven similar cases. He showed intense oedema, erythema and scaling of the face and neck. A mild case was seen at this time in a consultant colleague who showed an erythema behind the ears and slightly on the cheek ; he also had been using one of these soaps.

Since early February, 12 more cases have been seen in clinics. A further case was kindly referred to me from the far north of the county by Dr. R. B. Coles ; this

man is included in the patch test table. Two other patients have been admitted to hospital with facial exacerbations of an atopic and seborrhoeic dermatitis respectively. Although patch tests were positive and the same history of light-provocation and use of soap was present, they have not been included in the tables. None of the other cases was complicated by a co-existing dermatosis. Three " false " cases have been seen, one a bullous phototoxic reaction and two others probably due to contact dermatitis from other causes.

The Soap.

By mid-January, it had become apparent that these patients were all suffering from a dermatitis that was connected with the use of one or other of the two germicidal soaps. Enquiries at the manufacturers revealed that a new germicide, tetrachlorsalicylanilide (TCSA) had been incorporated in the two soaps mentioned for a period of about three months after a limited " consumer " trial in July. This soap had been withdrawn in October, three months before my approach was made to them. However, supplies would remain in wholesalers and retailers for a variable time. When cases continued to occur, the manufacturers went to the extreme lengths of withdrawing all bars of soap from shops in this and certain other areas in the country. Analysis of the soap used at the time the patient was seen (often some weeks after the onset) showed that TCSA was still present in the soap of six out of eight affected patients in February. Other germicides are now incorporated. The pH of the soap mainly used lies within the normal range for toilet soaps (*Which*, 1961).

The Eruption.

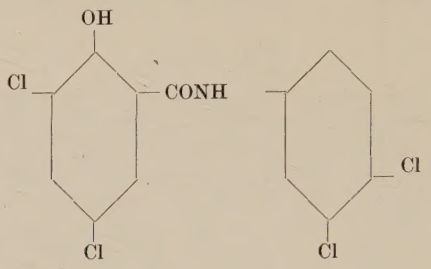
There was little variation in the clinical picture except in the extent and degree of involvement. The eruption began fairly suddenly though it might be preceded by some days' burning and pricking. In many cases the onset was dramatic and it was characteristic for this to occur at the weekend or after excessive or unaccustomed exposure on a bright day. Many recurrences took place over the fine Christmas weekend and several attacks followed prolonged exposure to an unusual degree of light. The variation in the value of light from day to day in the winter months is perhaps not fully appreciated. For instance, during the weekend of the 28 October it varied from over 200 kilolux on Friday to less than 40 on Saturday.

In the 24 clinic patients there has been a marked predominance of males (20); this may be because men wash their faces and necks more vigorously and more frequently; or because the particular soap is used more often by men. Most were outdoor workers. It is perhaps for this reason that so many cases have occurred in a predominantly rural area. One should also note that Buckinghamshire is relatively free from smoke and that the Chilterns rise to over 500 feet. Those workers who have indoor occupations have sometimes had to cycle long distances to work, or have had outdoor weekend hobbies.

The areas affected were those exposed to light and the eruption followed closely the light exposure area including the parting of the hair, bald areas or uncovered heads, the lobes of the ears, and even in one woman the protruberance of a double chin and the legs below the skirt. The hands were less frequently and less severely affected, but might show a rash on the dorsal surfaces up to the wrists or the elbows (in outdoor workers with rolled-up sleeves). The sawyers, bricklayers, and builders frequently wore open-necked shirts and showed intense erythema on the " V " of the neck. The back and sides of the neck were particularly affected and irritation and burning was noticed there after the face had recovered.

The initial symptom was burning, when severe, described as a " deep burning ". In those with an acute onset itching occurred but on the whole the rash was

very much less irritating than might have been supposed from its severity. The eruption was erythematous and not exudative. The initial stage was associated with a varying amount of oedema and then or at a later stage there might be intense swelling of the eyelids. The skin of exposed areas, particularly that of the neck, quickly became thickened. As the rash subsided and the erythema gave way to pigmentation, it closely resembled the thickened lichenified skin in atopic dermatitis.



TETRACHLORSALICYLANILIDE.

This substance was developed as a deodorant and bacteriostatic agent, having a wide range of activity against skin organisms. Its action is similar to that of such substances as chloroxylenol, hexachlorophene and quaternary ammonium compounds. It was patented in the United States in 1955 and is known also as " Irgasan BS 200 ". According to an article by Lennon, Furia and Zussman (1960) it has in the past two years been used in several consumer, industrial and detergent preparations here and abroad (U.S.A.). It is 95% pure, containing not more than 5% trichlorsalicylanilide. It is sparingly soluble in water but has a ready solubility in alkaline solution. TCSA has a characteristic ultra-violet absorption spectrum with a peak absorption of 360 mμ in ammoniacal methanol ; in acidic methanol, absorption shifts further into the ultra-violet region. The fluorescence is bluish for the ionized compound and yellow for the non-ionized form. I have been able to demonstrate on myself that in alkaline solution the fluorescence on the skin remains blue whereas in weak acidic solution or applied in a neutral alcoholic solution it quickly becomes yellow (non-ionized) and appears to fade more rapidly. This may have some bearing on its reactions in a soap solution. It is said not to be readily dehalogenated and to be resistant to hydrolysis. Photodecomposition in aqueous alkaline solution is catalyzed by oxygen. The light stability of solutions improves with the decreasing pH. Tests suggested that 10 to 20% of TCSA is adsorbed and retained on the skin. It may well be that excessive or frequent use produces an accumulation of this substance to an unusually high level or that its behaviour in parts of the skin liable to sweating under conditions of heat and light may influence its reactivity. Further investigations are necessary to confirm this and indeed the whole mechanism of the photosensitivity. The paper (from which most of these details are drawn) emphasizes that a very considerable number of tests, including over 350 " repeated insult patch-tests " on human subjects, hand-wash tests, and, of course, animal tests, did not reveal any untoward reactions and it was in fact considered safer than hexachlorophene in a comparable strength.

INVESTIGATIONS.

Patch Tests. These have been carried out on sixteen of the actively affected persons (see Table I) and on four earlier cases now clear of all but residual signs of the eruption. TCSA 1% in alcohol was supplied by the manufacturers of the soap. Two of the first

four cases tested produced a very strong reaction to this, and one a strong reaction, and it was therefore diluted to 0·25% or 0·1%. Patch tests to the same alcohol without TCSA were negative. Some delayed reactions were observed and strong reactions were still visible two weeks later. Tests were also carried out with solutions of the soap with and without TCSA, with a 1% solution of hospital soap and with trichlorsalicylanilide (TriCSA) about 0·2% (maximum solubility in alcohol). Among the reacting patients there were three affected workers from the factory. Positive reaction consisted of more or less intense erythema with oedema. In severe reactions this oedema presented as a wheal surrounding the central test area. After UVL provocation the wheal disappeared but the patch itself became more livid. Where patch tests were repeated in the fading stage, they were usually much less marked or only positive at a greater strength.

TABLE I.—*Patch Tests : Results in Actively Affected Persons.*

	Total tested	++	+	±	−
1% TCSA [alc]	4	2	2	0	0
0·25% TCSA [alc]	10	3	5	2	0
0·25% TCSA [oil]	2	1	1	0	0
0·1% TCSA [alc]	2	0	1	1	0
TriCSA 0·2% [alc]	6	0	0	3	3
1% Soap with TCSA	11	2	5	2	2
0·5% Soap with TCSA	3	0	1	1	1
1% Soap without TCSA	8	0	0	2	6
0·5% Soap without TCSA	6	0	0	0	6

± [mild erythema only) is interpreted as a doubtful or mild irritant reaction.

Twenty-seven normal persons were tested with 1% TCSA ; 26 were negative, but one patient, an elderly man in hospital with angina, produced a strongly positive reaction. He did not use these soaps but did use a cosmetic after-shave lotion containing some as yet unknown antiseptic. No reaction occurred in 15 persons tested with TriCSA ; one doubtful reaction occurred to 1% soap with TCSA and five mild reactions in 42 tests with a solution of the soap iteslf. These faded quickly and were considered to be irritant reactions. Bettley (1960) found that 21 out of 114 normals gave a positive reaction to 1% soap solution and a further 22 gave a dubiously positive reaction.

Five persons with other skin conditions (contact dermatitis, light sensitivity, rosacea etc.) were also tested with these substances. One equivocal reaction to 1% TCSA occurred ; the rest of the tests were negative.

Light-provoked patch tests. In 6 patients, reduplicated patch tests were provoked by a suberythema dose of UVR after 24 hours. No provocation of negative reactions to positive ones occurred, but the light-exposed patches remained more persistent and rather more marked in four of the six patients.

Exposure tests. A dab of 1% TCSA was applied to the forehead or cheek of 8 normal persons ; no reaction occurred. TCSA 1% was applied to 6 affected persons ; marked erythema and oedema occurred, usually within three hours. This persisted for several days—in one case for a week—as a scaly erythematous patch. TCSA 0·5% in one other patient, and 0·25% in another, produced a positive reaction in three patients and no reaction in another. TriCSA produced no reaction. The results parallel those of the patch tests. I applied 1% TCSA to my own forehead and ear for ten consecutive days without effect ; but two days ago, after a pause of some ten days, a further application produced a typical positive reaction.

Histology. A section taken from the neck of an affected person showed hyperkeratosis, some parakeratosis, moderate acanthosis but no spongosis. There was a

very intense dermal lymphocytic infiltration—in places almost " nests " of lymphocytes—mostly perivascular but also around the sweat ducts. The changes are similar to those described for allergic solar dermatitis by Wright and Winer (1960).

Comment.

This outbreak of photodermatitis presents several unusual features. The halogenated salicylanilides have not hitherto been regarded as photosensitizers, though halogen-substituted fluoresceins are photodynamic substances (Blum, 1941). Preliminary patch tests involving more than 350 subjects, including a great number with skin ailments, and other tests (Lennon, Furia and Zussman) suggested that TCSA was no more an irritant or potential sensitizer than comparably effective concentrations of bisphenols. Nor have there been, apparently, any reported cases of adverse reaction in the two or three years in which this substance has been used in commercial soap and detergent preparations. But I have shown that it took me several months—and a chance finding—to indicate that it might be the cause of these cases of photodermatitis. At the same time as my first case occurred, Dr. G. C. Wells had also seen a similar case in London, but by ill-luck the patient had used the less popular of the two soaps. We are not used to thinking in terms of sensitization dermatitis from soap. On the basis of the considerable preliminary tests, it would have been impossible, I think for any dermatologist to have advised against the use of this substance, or to have predicted the likelihood of a photodermatitis. The only clue lay in its fluorescence since we are apt to regard fluorescent substances as potential photosensitizers.

The results of the tests so far carried out—and these are as yet incomplete—suggest that the photodermatitis is due to the tetra-chlor compound but not the tri-chlor compound. Since up to 20% TCSA is said to be adsorbed on to the skin, it is not unreasonable to think either that one of the chlorine ions is unstable and become free to combine with the keratin, or that a degradation product of TCSA occurs under the influence of light. The difference in the fluorescence of the ionised and unionised form, and the apparent persistence of the former in alkaline solution, invite further study. Wynn-Jones (1961) found 12 cases in a large general practice in a month ; the proportion of workers affected in the factory was nearly 30%. The very considerable amount of soap used by these workers presumably increased the amount of adsorption on to the skin.

Patch tests were positive at low dilution without provocation by U.V.R. A minimum of light may be necessary for the initiation of the sensitization, or light of the correct wavelength for its manifestation. The mechanism appears to be similar to that found by Calnan (1957) in lipstick cheilitis due to tetrabromofluorescein. But, unlike eosin, the few repeated patch tests carried out so far on early cases no longer active have shown a reduction in the level

of reactivity to TCSA and this has been accompanied by freedom from exacerbations in bright light. Tests are being carried out also to attempt to determine whether the reaction is of photodynamic or photoallergic type.

Epstein (1960) considers that the combination of a plain contact sensitivity and photosensitivity is to be regarded as a double sensitivity—" a peculiarity of the phenothiazines "—but I feel uneasy at accepting this as an explanation for these cases, all of which showed such characteristic and uniform features. Further patch testing of persons who have used these soaps may bring to light cases in which plain contact sensitivity is shown by patch tests in the absence of photodermatitis ; in that case the argument for a double sensitivity becomes more valid. Meanwhile we should pursue investigations in the affected cases in the hope of throwing further light on to a mechanism that is still obscure. In this way we may be able to predict more reliably what compounds are likely to give rise to reactions that have proved as embarrassing to the manufacturers of the soap as they have been distressing for the patients.

Summary.

An account has been given of an outbreak of 53 cases of photodermatitis due to tetrachlorsalicylanilide incorporated in a soap. Mention has been made of the unique nature of an extensive outbreak of cases in a factory.

Patch tests gave a strongly positive reaction in 16 out of 22 patients and a mild positive in three cases at 1% or 0·25% strength : 6 out of 7 cases reacted to 0·1% but none out of 4 recovered cases reacted to the weaker strength. No reaction occurred in 26 out of 27 normal persons.

Exposure tests followed the same pattern and provoked the eruption at the site of application in affected, but not in normal persons. The nature of the reaction and the problem it presents are obscure. The possibility of TCSA being present in other cosmetic preparations is mentioned.

My thanks are due to Dr. G. Wynne-Jones, Factory Medical Officer, for his most careful and comprehensive records and assistance in the factory outbreak ; to Mr. J. McL. Philp for his co-operation and help, and to my registrar, Dr. M. Walshe, who helped to carry the numerous patch tests.

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Postscript.—A further eleven cases have since been seen. Some patients whose eruptions cleared on ceasing to use the soap are no longer intolerant to light.

PHOTOSENSITIVITY DUE TO PITCH.

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THE amount of disability caused by " smarts " due to photosensitivity to pitch seems to vary ; for instance, Jenkins (1948) said that gas workers seldom troubled to report it, whereas in the outbreak described here, frequent complaints resulted.

Finding the action spectra for substances such as pitch would seem to have practical as well as theoretical importance, for, if known, it is conceivable that the photosensitivity might be controlled by the application of a light barrier, as advocated by Williamson (1960). Action spectra should also be of use in identifying the photosensitizers. This follows from the Grotthus-Draper Principle, viz., the action and absorption spectra of a photosensitizing substance are the same. As absorption spectra are widely used for identification, if therefore the action spectrum of pitch is known, it should be possible to identify the photosensitizer it contains.

It has generally been assumed that spectral reactivity of pitch and tar was mostly in the long wave ultra-violet and visible spectrum, an unsatisfactory region for light barrier applications. Williamson recently quoted the main action spectrum as lying between 390 and 500 mμ, the figures being those of Foerster and Schwartz (1939). Similar findings were reported by Peukert and Koehler (1940) and Bayer (1942). The photosensitizers in pitch are thought to be compounds like acridine, anthracene and phenanthrene (Burckhardt, 1939 ; Foerster and Schwartz, 1939). The whole subject was well reviewed by Koelsch (1926) and more recently by Schwartz, Tulipan and Birmingham (1957).

Our paper describes an attempt to determine the action spectrum of pitch for skin erythema with the aid of a monochromator. Some other related clinical and experimental observations are also presented. In our experimental work, tests of radiation of full spectrum, with and without filters, as used by earlier workers, were found to be unsatisfactory. Only our results with a monochromator will be considered (Magnus, Porter, McCree, Moreland and Wright, 1959). The work was prompted by one of us (K. D. C.) having under his care a number of cases of photosensitivity from pitch fumes arising in an industrial

process. For various reasons we were able to test only one of the workers with the monochromator ; for further study we have had to use normal volunteers.

The factory concerned was engaged in moulding various articles from a hot mixture of pitch, asbestos and slate dust. After mixing, and before moulding, the hot plastic mixture was rolled and beaten with iron bars and it was during this and the actual mixing that the main exposure to fumes occurred. The amount of fumes was great since the exhaust ventilation system was highly inefficient in spite of some effort to improve it.

The ill effects of pitch and tar upon the skin, described first by Lewin (1913), include photosensitivity as well as the production of comedones, folliculitis, pitch warts, keratoses and epitheliomata ; they are too well known to need description here. Certain facts, however appear to be less generally appreciated. First, apart from evidence of light sensitivity, which was our main concern, it was of interest to note that the acneiform eruption, which occurred when the skin was exposed to pitch fumes was different from that produced by the friction of clothing contaminated with pitch. In 70% of those exposed, pitch fumes produced a pure eruption of comedones, almost entirely confined to the ears and face, particularly the malar areas ; whereas in 40%, the lesions on the thighs were those of folliculitis but not comedones. In no case were there inflammatory lesions on the face or blackheads on the thighs. Second, the photosensitivity reactions included the " smarts ", which are the subject of the experimental work, melanosis and photophobia. The last, which occurred in about 40% of men exposed, was a smarting and watering of the eyes when exposed to light and was thought probably to be due to a similar mechanism as that producing the " smarts " on the skin. Third, when first examining these workers, it was obvious that the light exposed skin of a large number was much darker than normal. Although initially it was assumed that this was due simply to an increase in melanin in the skin, it later became clear that there was a second factor, viz. retention of pitch by the skin, presumably in the pilosebaceous follicles. This was well known to the men, for some 55% of them insisted that they always " sweated " a yellow material which stained clothing and bed linen. During their two weeks summer holiday, this staining gradually disappeared, usually within three to seven days, although in about 25% it was still apparent after two weeks. It was well known to their families and friends that their skins lightened progressively during holidays and there is no doubt that some of the depth of colour, in some cases perhaps all of it, was due not to melanin but to pitch.

The " smarts " themselves, which were the men's main, and in many cases the only complaint, were intense smarting and burning sensations associated with erythema occurring after exposure to light. What is not generally known is that not only does the smarting almost invariably precede the erythema but that in some cases it occurs without any erythema at all. In most cases direct

sunlight was required to elicit the response and in a high proportion the summer sun, the reaction disappearing during the winter in the vast majority. In a few of those more severely affected, bright diffuse daylight was capable of causing smarting. Most men found window glass no protection, which suggests that the active wave-lengths included those of over 320 mμ, the latter being the approximate lower limit of transmission of ordinary window glass. About 70% of the white workers suffered from " smarts ", whilst Indians and negroes, of whom there were ten, were all apparently immune. In those affected, the intensity of the responses was directly related to the degree of exposure ; 40% were mild, 16% moderate and only 14% severe. The smarting sensation usually appeared within fifteen minutes of exposure and disappeared by one half to four hours after gaining the shade. In a few, however, it was twelve hours or so before all burning ceased. When no longer exposed to the pitch, most men found that they continued to smart on exposure to intense light for one to three days. This presumably had a direct relationship to the leaching from the skin of the yellowish staining substances previously mentioned. It is of some interest that there was a latent period between first exposure, even gross, to the pitch fumes and the development of " smarts ". This latent period never appeared to be less than two weeks and in many cases was a good deal longer.

As the ingredients of pitch and tar are commonly characterized by their boiling points, it might have been useful to know the temperature of the ovens in the factory in narrowing down the search for the photosensitizers. Unfortunately this was not known.

Investigation

The worker examined with the monochromator was a man aged 44 who experienced severe " smarts " when exposed to sunshine during the summer. They affected the face, backs of the hands and forearms and were accompanied by erythema. It took twelve hours for the burning sensation to go away after leaving the sun and during his holiday his photosensitivity ceased altogether after the first three days. He had blackheads on the malar areas, nose and cheeks, but no other abnormality of the skin. General physical examination was normal. Uroporphyrin was not detected in the urine. Faecal porphyrins were normal.

Pitch from the factory was powdered and suspended in chloroform, the pitch settling as a black deposit and leaving a pale yellow chloroform layer above. The mixture was always well shaken before being applied to the skin and its concentration kept approximately constant by ensuring that the volume of the deposit was about a quarter that of the chloroform layer.

Usually the skin was painted twice daily for two to three days before irradiation with the monochromator. Immediately before irradiation the skin treated with pitch was cleaned with ethanol so as to reduce light barrier effects but also to enable erythemal reactions to be observed. Control skin was painted with chloroform only and, immediately before irradiation, cleaned with ethanol. The skin sites used were either the inner aspect of the forearm, one limb being treated with pitch and the other used as a control, or the back, one side being treated with pitch and the other used as a control. A similar procedure was used with liquor picis carbonis B.P.C., crude coal tar (North Thames Gas Board), acridine (Hopkin and Williams) and anthracene

(Eastman Kodak). The monochromator light tests were performed using the method of Buck, Magnus and Porter (1960). This allows the determination of minimal erythemal dose (MED) throughout the spectrum, but can only be used on a relatively large area such as the back. In certain experiments, only the limits of abnormal spectral reactivity were investigated and no attempt was made to ascertain the MED throughout the spectrum ; this applied to the case of the factory worker, who could not spare time for detailed studies and also to experiments where the forearm was used in normal volunteers.

Results.

(i) *Tests on pitch worker.*—In the factory, contamination of the skin with pitch occurred from vapour. This could not conveniently be imitated in the laboratory and the man's skin was painted with the pitch-chloroform mixture described above. Exposures were given at 10 mμ intervals from 320 to 450 mμ, and at 500, 550, 600, 650 and 700 mμ. Regrettably there was no opportunity to study this man's skin reactions to the region 250–310 mμ. This worker alleged that skin painted with pitch smarted when radiation in the range 340–430 mμ was used from the monochromator. Whenever this was felt, which generally appeared within five to ten minutes after the test had started, a strong erythemal reaction was always seen immediately after the completion of the exposure. These erythemal reactions persisted for at least forty-eight hours ; unfortunately it was not possible to observe them longer. Some of these abnormal erythemal reactions developed slight oedema about eighteen hours after the irradiation, but this subsided after another six to twelve hours. No urticarial response was seen, or pigmentation within the period of observation. Tests on control skin were always without effect.

The man stated that the burning sensation, which he noticed when spectrally reactive radiation was used from the monochromator, closely resembled the " smarts " he experienced at work. This statement at first was received by us with considerable reserve, but subsequent experiments on normal volunteers led us to believe him.

(ii) *Tests on normal volunteers.*—Monochromator tests were performed on three normal volunteers who had painted one forearm with the pitch-chloroform mixture twice daily for four days. On the fifth day the excess pitch was removed with ethanol and the area irradiated.

With the first subject, aged 38, of moderately fair complexion and who burnt easily and tanned poorly with sunlight, an exposure at 360 mμ was made. After seven minutes, smarting and pricking were felt in the irradiated area, the test was stopped and the site examined. No visible change was observed, although the irradiated area continued to smart for about three quarters of an hour. Another exposure was made near the previous irradiation site for fifteen minutes with the same waveband ; again smarting was felt after approximately seven minutes. At the end of fifteen minutes exposure a strong immediate erythema was visible. This persisted for ten days, after which it faded, leaving

no other change except very mild pigmentation. The control forearm was also irradiated at 360 mμ for fifteen minutes. This led to no subjective sensations, but immediately after the irradiation had been completed a faint erythema was visible, which faded completely within three minutes. No other visible change was observed, although the area was examined daily for the next three weeks.

With the second subject, aged 30, with a very fair complexion and who was very susceptible to sunburn and did not tan, exposures were made at 360 and 400 mμ for fifteen minutes each. Again, although the subject was unaware that it might occur, smarting and tingling were reported about five minutes from the start of the exposure. Both irradiations resulted in strong immediate erythemal reactions which, about two minutes later, were replaced by small but quite definite urticarial wheals. These persisted for approximately an hour, and on subsiding showed erythema only, remaining for about seven days. No pigmentation was observed in this subject. Tests on control skin were entirely negative.

With the third subject, aged 25, who had a darker complexion, striking urticarial wheals and erythemal reactions, together with smarting, were produced on forearm skin treated with pitch and irradiated with the monochromator for fifteen minutes at wavelengths from 340 to 400 mμ. Again, smarting generally appeared after five to seven minutes exposure with each wavelength and immediate erythemal reactions were observed which turned, after two to five minutes, into urticarial responses lasting about an hour. These were replaced by erythema persisting for over a week. In this particular subject, who normally tanned well with sunlight, striking pigmentary changes could be seen after about two days at the sites of the monochromator tests. This subject also occasionally showed "immediate pigmentation" in control exposures, this effect remaining visible for only a day or two.

Each of these three subjects was also tested with 360 mμ radiation at intervals to determine the length of time skin treated with pitch remained photosensitive. Exposures were made every two or three days using the same dose. In the two subjects who reacted with an urticarial response, this was obtained, though much reduced, for the next six to eight days. For about ten days following, only erythemal reactions were seen. In the subject who reacted with erythema alone, this reaction was obtainable, gradually weakening, for a period of twenty days after the application of pitch.

(iii) *The action spectrum for erythema due to pitch.*—Three volunteers, aged 50, 25 and 38, took part in this experiment. Exposures of graded duration were made on the back on treated and control areas, at intervals of 10 mμ in the spectrum from 250 to 450 mμ, and also at 475, 500, 550, 600, 650 and 700 mμ. The test sites were examined at approximately six hour intervals for the first twenty-four hours and subsequently at longer intervals.

The results were somewhat variable but all subjects showed photosensitivity and experienced smarting in the long ultra-violet and adjoining visible spectrum.

The results obtained in one of the subjects are shown in Fig. 1. When erythemal reactions were seen in skin treated with pitch, they usually appeared immediately or very soon after irradiation with the wavelength region 330–440 mμ. Within this region urticarial responses were frequently observed, the whealing generally appearing about two minutes after the exposure had been completed and was associated with smarting during and for a short time after the exposure. The

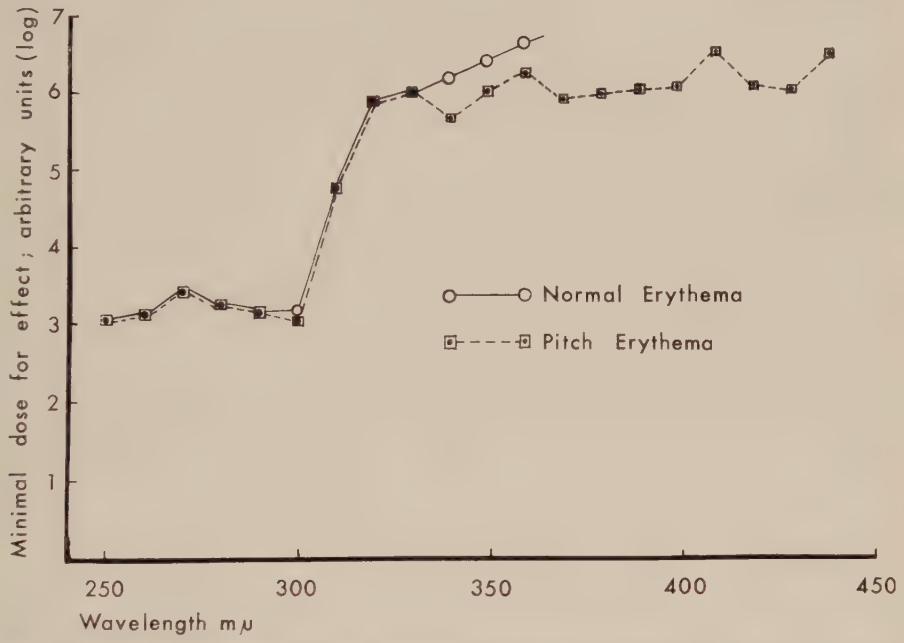

FIG. 1.—Graph to show relative dose of radiation causing just perceptible erythema (MED) on normal skin and on skin treated with pitch. Wavelengths used 250–700 mμ. Pitch lowered the MED significantly from 340 to 360 mμ and caused erythemal or urticarial responses from 370 to 440 mμ, in which region untreated skin was unreactive (exposures up to one hour) in this particular subject.

wheals showed no definite flare. When they subsided they were replaced, generally within three quarters of an hour, by erythemal reactions of the size of the exit slit of the monochromator. These persisted for several days and were frequently associated with pigmentation, appearing two to three days after the irradiation.

Pitch never produced smarting or significant lowering of MED in the visible spectrum with wavelengths over 450 mμ, in the sunburn spectrum (280–320 mμ) or in the shorter ultra-violet. However, slight lowering of MED occurred at 260 mμ in one subject and at 300 mμ in the two others. In the last instance, in one subject irradiation had been started at 700 mμ, working down to the shorter wavelengths. When 300 mμ was reached, a diffusely distributed peri-

follicular erythema was noted in the whole area treated with pitch. By that time, this had had over twenty paintings. Evaluation of the significance of the slight reduction of MED at 300 mμ by pitch is therefore difficult in this case ; whether it was merely because ultra-violet light was acting on skin already irritated or was due to true photosensitization could not be decided. Further tests were abandoned on this particular person.

In the subject aged 25, pitch did not decrease the MED in the range 270–340 mμ, but did at 350–420 mμ. At 260 mμ the MED was slightly lowered also. With wavelengths above 340 mμ he seldom produced erythemal reactions at all on control skin, though frequently " immediate pigmentation " was seen.

(iv) *The spectral reactivity of liquor picis carbonis and of crude coal tar.*—Two subjects only were studied. Liquor picis carbonis B.P.C. was painted on to the inner surface of one forearm daily for about one week, the skin being wiped with ethanol just prior to irradiation and exposures made at 10 mμ intervals from 320 to 400 mμ, and of fifteen minutes' duration each. Erythemal reactions were observed and smarting experienced at wavelengths between 340 to 380 mμ in both subjects and also at 400 mμ in one of them. The erythemal reactions persisted for three or four days and showed subsequent pigmentation. Control irradiations on untreated skin and also on skin painted with tinct. quillaiae B.P., the emulsifying agent in liquor picis carbonis, were negative, except for the occasional observation of " immediate pigmentation ". The experiment with crude coal tar was entirely negative. Here, the tar was applied to the forearm for one week, renewed as necessary to ensure the test area was completely covered, and removed sufficiently with ethanol for erythemal reactions to be seen, just before irradiation with wavelengths from 320 to 400 mμ.

(v) *Preliminary tests for the spectral reactivity of acridine and of anthracene.*—Three subjects took part. Acridine, 10% in chloroform,and anthracene, approximately 2% in benzene, were used. Control areas were treated with chloroform and with benzene respectively. The test substances were each painted on to the forearm twice daily for two days. As before, the skin was cleaned just prior to irradiation, though this was not necessary for the observation of the reactions. Exposures were given at 10 mμ intervals in the spectrum from 300 to 450 mμ. Erythemal reactions were obtained with acridine in only one subject from 340 to 380 mμ. The other two subjects showed no reactions. With anthracene, however, striking urticarial responses with smarting were regularly obtained in all three subjects from 340 to 380 mμ, whereas reactions in no way different from control tests were obtained with sunburn radiation (280–320 mμ). Erythemal reactions appeared on the subsidence of the wheals and persisted for several days, in one subject, leading to increased pigmentation after two to three days.

(vi) *Some factors controlling the mechanism of photosensitivity.*—A few tests were performed on normal subjects to ascertain the effect of oral antihistamines

and of reduced oxygen supply on the photosensitizing action of 360 mμ radiation on skin treated with pitch and anthracene respectively.

First, it was found that the erythemal and urticarial reactions and smarting produced with anthracene and 360 mμ radiation in two subjects were quite uninfluenced by 12 mg. of chlorpheniramine maleate (Piriton) taken by mouth four hours previously ; this also obtained when the dose was raised to 24 mg.

Second, in order to reduce the oxygen tension in forearm skin previously prepared with pitch or anthracene, a sphygmomanometer cuff was placed on the upper arm and the pressure raised well above the systolic. This was maintained for five minutes before irradiation was started and continued throughout the exposure, which lasted for fifteen minutes. At the end of the exposure the blood flow was restored but no erythemal reaction was seen or smarting experienced. When exposure was repeated a few minutes later with normal blood flow, smarting and an urticarial reaction occurred. Repeated on two other subjects the same results were obtained.

It was also observed in two further subjects, who as far as they knew had never been in contact with anthracene before, that this substance need only be painted on the skin about one hour before irradiation for photosensitization to occur ; both smarting and erythema were produced. With pitch, smarting could be produced on irradiated skin, using 360 mμ, three hours after a single application, but to obtain erythema with the monochromator more than one painting seemed to be necessary.

Discussion.

The conclusions of early investigators as to the active wavelengths in photosensitivity due to pitch and allied substances do not differ essentially from ours obtained with a monochromator, allowance being made for different experimental techniques and variations in composition of the substances tested. Foerster and Schwartz suggested 390–500 mμ was the main active region, whereas in our experiments reactions in skin treated with pitch could readily be obtained with our monochromator within most of the region 330–440 mμ, though the limits of spectral reactivity varied slightly in each of our subjects.

Action spectra, that is, plots of the values of the normal MED less that of the pitch MED, could only be constructed for a small part of the spectrum from data from two persons, (Fig. 2) because of failure to produce erythema in untreated skin over much of the spectrum in which pitch was active. This graph suggests that photosensitization has one maximum at 340 mμ, which might be due to anthracene, as it has a peak of absorption at this point. But anthracene also has peaks at 355 and 375 mμ (Mayneord and Roe, 1935). However Fig. 1 strongly suggests that several photosensitizers must be present in pitch, as Foerster, Schwartz and Burckhart were well aware. Anthracene and acridine, for instance, cannot be the sole photosensitizers, as their absorption

spectra are confined to the ultra-violet. Furthermore, the deduction of absorption spectra from data obtained from action spectra, and hence arrival at the identity of photosensitizing substances must be used with caution. Not only must one be wary of the considerable experimental error inherent in work on biological material, but one cannot always be sure that absorption and action spectra necessarily coincide ; in fact it seems that the Grotthus-Draper Principle may not apply in all cases. Work from this laboratory on the furocoumarin,

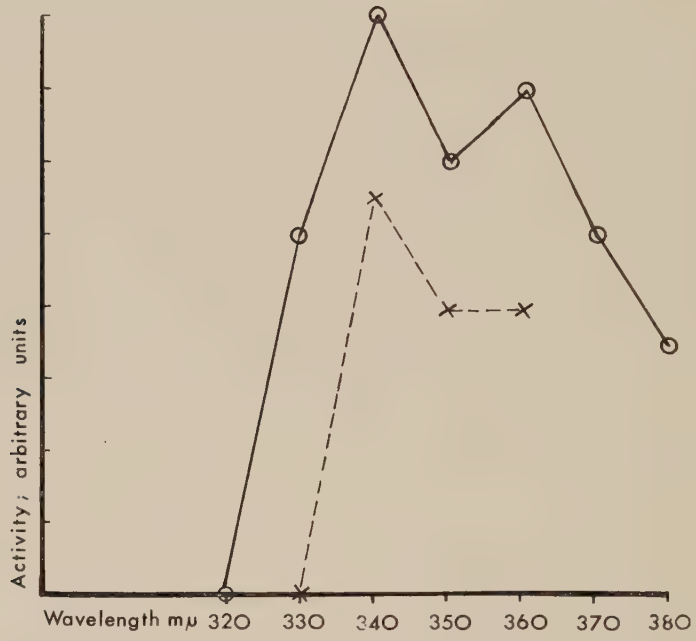

FIG. 2.—Action spectra for erythema due to pitch from data obtained on 2 normal subjects. In the ordinate scale, activity = normal MED *less* pitch MED. Two subjects showed maxima at 340 mμ and one of them a maximum at 360 mμ. Although reactions occurred at longer wavelengths on pitch-treated skin, the corresponding normal MED values were not obtainable in these particular subjects.

8-methoxypsoralen, by Buck *et al.* (1960) and the study of the wavelengths activating fluorescence in this compound by Pathak and Fellman (1960) are especially relevant. It should be noted that its absorption and action spectra are quite different and, that it may be chemically excited by wavelengths other than at its absorption maxima. Conclusions as to the identity of the photosensitizers in pitch drawn from studies of action spectra must therefore remain provisional.

Objection may be made to the fact that in our experiments we painted pitch on to the skin instead of administering it as fumes. This does not duplicate the factory conditions, and probably substances were present in the chloroform-

pitch mixture we used that were absent from the fumes. This could account for certain discrepancies between our clinical and investigative observations. For instance, our experimental studies of the length of time that photosensitivity persists, suggested that once pitch was applied, photosensitivity to 360 mμ irradiation remained for about three weeks. In the factory this period was usually three days, resembling the finding of Fleischhauer (1930) with " lianthral ". Three weeks, however, corresponds roughly with the time that has been estimated for the complete renewal of the epidermis of the forearm (von Volkmann, 1950). This coincidence of time might suggest that the photosensitization occurred by fixation in the lower epidermis, for, when malpighian cells were transformed into horny squames and were shed, it would be expected that photosensitivity would be lost.

An urticarial reaction similar to what we observed on irradiated skin previously treated with anthracene and pitch was noted by Foerster and Schwartz. They called it a " triple response ". From this one would infer that an " H-substance ", perhaps histamine, was liberated. But this seems doubtful, as chlorpheniramine failed to suppress the reaction, in which respect it would appear to resemble the sunburn response (Partington, 1954). Further, the urticarial reaction that we observed could not satisfactorily be described as a triple response, as, unlike Foerster and Schwartz, at no time have we seen a flare, though this might be due merely to some difference in experimental technique. If the chemical mediator is not histamine, its nature remains obscure.

Our results of the study of the role of the skin oxygen tension in the photosensitization process would seem to confirm previous work, suggesting that it is due to a photodynamic action, where the word "photodynamic" is used in the restricted sense of a photo-oxidative reaction (Blum, 1941). Constriction of a limb with a sphygmomanometer cuff, it is known, does not remove the oxygen completely, but merely reduces it (Naylor, 1960). Nor, of course, is oxygen the only material carried in the blood that would have its supply to the skin altered by such a procedure. If pitch and anthracene photosensitivity is due to a photodynamic action, evidently the reduction of oxygen by the cuff is sufficient to interfere with the development of observable lesions associated with smarting. In this respect the whealing reaction differs from that which we have seen in cases of solar urticaria. In our experience, obliteration of the blood supply in solar urticaria merely delays the appearance of the wheal, in the way described by Lewis (1927) for the histamine wheal. Further, the reactions of pitch and of anthracene would seem to differ in mechanism from those provoked by 8-methoxy psoralen, which we have found to be completely uninfluenced by restriction of skin blood supply with a sphygmomanometer cuff. This does not mean that the furocoumarins cannot be photodynamic, but only signifies that they might be photodynamic at low oxygen tensions.

Our demonstration with the monochromator of photosensitization to liquor

picis carbonis confirms Burckhardt's observation with liquor picis detergens ; our failure with crude coal tar is perhaps surprising. Possibly the former was active because it is an alcoholic emulsion, presumably favouring penetration into the skin.

Our tests of the spectral reactivity of acridine and anthracene are no more than preliminary explorations into the problem of the identity of the photosensitizing ingredients of pitch. To test all these for photosensitization is a very long task. It may be noted however that our results for action spectra in acridine and anthracene would seem to correspond fairly well with their regions of absorption in the longer ultra-violet (Mayneord and Roe, 1935 ; King, Gilchrist and Tárnoky, 1946). It should be noted that the whealing response and subsequent eczematous reaction Foerster and Schwartz obtained with acridine were not observed by us and that only one subject out of the three we tested showed photosensitization with this substance. Anthracene would seem to be more potent from our results so far. But as we have not yet studied the effects of benzpyrene, pyrene, phenanthrene and fluoranthane, which these workers and Burckhart (1939) found to be photosensitizing, we cannot come to conclusions as to their comparative activity. Some of these compounds, being powerful carcinogens, especially 3,4-benzpyrene, would be unsuitable for experiments on man. The short period of time required between application of anthracene and the production of experimental photosensitivity is to be expected with a photodynamic substance. This was not the case, however, with the pitch workers, who required two weeks' or more exposure to fumes before becoming photosensitive. Our experimental observation was, however, anticipated by Fleischhauer (1930) with " lianthral "; she noted that, only ten minutes after its application, photosensitivity could be produced.

It is possible that some may be tempted to assign the two or three weeks latent period of the pitch workers' photosensitivity to some sort of " allergy ". But the delay in becoming photosensitive is more simply explained by assuming that this time was required before enough pitch fume had accumulated in the skin. Photosensitivity due to chemicals has been plausibly, if tentatively, blamed on " allergy " by a number of writers, e.g. Schulz, Wiskemann and Wulf (1956) and Harber, Lashinsky and Baer (1959). However Schulz and his colleagues showed chlorpromazine to be photodynamic as well as considering it " photo-allergic ". Sulphanilamide also seems to be photo-active through more than one process Epstein. (1939), Blum (1941*b*), Burckhardt (1941) and Brodthagen (1958) have made interesting contributions in this field ; for instance, Burckhardt found that sulphanilamide may be photo-active at wavelengths outside its absorption spectrum, and Brodthagen, to whom credit must be given for the first report of photosensitivity due to chlorothiazide, made the intriguing observation that persons taking this drug may excrete in the urine a photosensitizing substance, at present of unknown constitution.

The pathological effects of light are obviously complex and difficult to study and it will not be surprising if more than one mechanism is shown to exist in photosensitivity due to chemical substances. What is clear is that very little is definitely known and that more work of a fundamental nature is required. At the moment the only hypothesis, which seems to have reasonably satisfactory evidence to support it, is that of photodynamic action (Clare, 1956); pitch photosensitivity, our evidence suggests, may be due to this.

Practical Implications.

It is clear from the experimental results that a satisfactory light screen cannot be devised, unless it is to contain a reflectant substance such as zinc oxide, which would make the preparation unacceptable to most factory workers (cf. Williamson, 1960).

If exhaust ventilation fails, it seems more logical to try to remove the pitch from the skin and so prevent its ill effects. To this end a very small pilot trial was organized on six of the worst affected men, using a waterless skin cleanser containing terpene and xylene, followed by thorough washing with soap and water. It was planned to follow this cautiously, if no skin irritation resulted, with a larger trial. Unfortunately at this point the factory was taken over and moved to the Midlands. In the end only four men underwent this trial, and the results therefore were inconclusive, although they did suggest that this was a highly promising line. It should be noted that Williamson, who recommended the use of a light barrier cream for tar photosensitivity, also advocated thorough washing. We suspect that the latter is likely to be the more efficacious.

Summary.

An outbreak of photosensitivity due to pitch fumes in an industrial process is described and certain clinical features emphasized.

A monochromator was used for action spectrum studies on skin which had been previously painted with pitch. Abnormal spectral reactivity was obtained on a worker exposed to pitch in the region 340–430 mμ. Similar results were also found in three normal volunteers.

The sunburn spectrum (280–320 mμ) and shorter wavelengths down to 250 mμ do not seem to play an important part in the photosensitization process.

Reactions on skin treated with pitch, and produced with appropriate wavelengths from a monochromator, were erythematous, urticarial and subsequently pigmentary.

A subjective sensation, usually smarting in character, was commonly associated with experimental pitch photosensitization. It appeared during and shortly after irradiation, was generally followed by an urticarial response, sometimes only by erythema, and occasionally occurred without visible changes in the skin.

Similar objective and subjective responses with light were obtained with anthracene, and, to a lesser degree, with acridine.

The urticarial response and its associated smarting sensation, due to photosensitization with pitch or with anthracene, was not prevented by chlorpheniramine ; it is provisionally postulated that histamine might not be the chemical mediator.

Results were obtained which seem to confirm the view that pitch and anthracene were " photodynamic " substances, i.e. photosensitization probably required the presence of molecular oxygen.

Practical measures for the prevention of pitch photosensitivity are briefly discussed.

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PHOTOSENSITIVITY DUE TO CERTAIN DRUGS.*

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The experimental findings in the cases reported here may help to elucidate the mechanism of the production of light eruptions due to drugs.

Investigation.

All tests were carried out in pairs on the back of each patient. One test area was then exposed to the rays of the sun twenty-four hours later (the responses are more pronounced than with quartz lamp). Results were read daily for seven consecutive days. The areas of positive simple tests to phenergan (promethazine) and largactil (chlorpromazine) were exposed after forty-eight hours. Promethazine was used as a 2·5% solution for intramuscular use and as 2% ointment. Chlorpromazine was used in 2·5% solution for intravenous use.

Case 1.—A woman, aged 40, was given hydrocortisone and tetracycline ointment and dragées of promethazine to take three times daily for lichenified eczema of the right leg. On the seventh day, after normal exposure to May sunlight, a diffuse erythema with slight oedema appeared on all exposed parts of the body. The redness subsided after four days. A patch test with promethazine powder was then carried out, showing after twenty-four hours strong erythema and oedema, which within the next twenty-four hours after a casual exposure to sunlight developed into large vesicles. There was also a recurrence of the eruption at all previously affected sites. The patient was then referred to me for further investigation. Erythema again subsided completely within the next five days.

Skin Tests.—Patch tests with promethazine were positive only after forty-eight hours. There was intense oedema but no visible vesiculation. In ten controls these concentrations never produced any reaction on the skin. In addition, the patient was tested with chlorpromazine, with sulphanilamide powder—by both patch and scratch tests, and with novocaine and paraphenylendiamine. There was a positive reaction with vesiculation to the latter only. After the exposure to light, test reactions from promethazine became more oedematous, but no visible vesiculation was seen. The surrounding area became redder. Reactions from chlorpromazine consisted of redness and swelling. Other tests were unchanged.

Histological examination.—Biopsy specimens were taken from the areas patch tested with promethazine and chlorpromazine and subsequently exposed to light seventy-two hours after the patch tests were performed. Spongiosis with oedema and perivascular infiltration in the dermis composed mainly of lymphocytes was found in reactions to the former drug ; only perivascular infiltration with no gross changes in the epidermis was found in the latter.

She could walk in sunshine with impunity after a week. Three weeks later, patch tests were performed with the solution of promethazine which had deliberately been left exposed to sunlight for seven days and which had turned bluish-black and also with the usual promethazine ointment. Both patch tests were positive and were aggravated by exposure to light. The patient experienced irritation in the previously affected sites.

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Case 2.—A woman, aged 41, took three tablets of sulphaguanidine in a period of two hours. Seven hours later by the afternoon of a sunny day she noticed diffuse redness of the uncovered parts of both arms ; the redness of the face assumed a bat's wing distribution. The following day, after a short exposure to sunlight, the redness became so intense that it necessitated a short treatment with prednisone. After two weeks she could walk freely in the sun.

Skin tests.—Patch and scratch tests were carried out with sulphanilamide, sulphathiazole and sulphaguanidine, and patch tests with promethazine, chlorpromazine, novocaine and paraphenylendiamine. Only the patch and scratch tests from sulphanilamide were positive, the latter with visible vesicles. After the light exposure, the patch tests areas showed increased redness, oedema and vesiculation. Patch tests with promethazine and chlorpromazine followed by exposure to light were positive, erythema and oedema being visible. Others with light were negative.

Histological examination.—Biopsy specimens were taken from the areas of patch tests with sulphanilamide and promethazine solution subsequently exposed to light forty-eight hours after the performance of the test. The former showed spongiosis and intraepidermal vesiculation. In the upper corium there was a predominantly perivascular infiltrate ; slight intercellular oedema with vasodilatation and mainly perivascular infiltration composed of lymphocytes was seen in the latter.

Case 3.—A housewife aged 34 developed an erythemato-papular eruption of the uncovered parts of hands, arms and sternoclavicular triangle on the seventh day of treatment with promethazine by mouth.

Skin tests.—Patch tests with promethazine and chlorpromazine, and patch and scratch tests with sulphanilamide, were negative. Patch tests with promethazine and chlorpromazine subsequently exposed to light showed erythema, oedema and infiltration. Histological examination of the area tested with promethazine exposed twenty-four hours later to light revealed only oedema and vasodilatation with lymphocytic infiltration in the dermis. No spongiosis was seen.

Case 4.—A man aged 43, a manual worker, after taking chlorpromazine tablets for four days noticed scattered papules on the trunk, i.e. parts not exposed to sunlight.

Skin tests.—A patch test with chlorpromazine was positive, while that with promethazine was negative. After exposure to light, the patch test with chlorpromazine showed definite though only slightly increased redness ; the test with promethazine also became positive.

Histological examination.—Biopsy specimens were taken from the chlorpromazine and promethazine test sites after seventy-two and forty-eight hours respectively. The former showed an eczematous reaction with small abortive vesicles, while the latter exhibited only oedema, vasodilation and perivascular infiltration composed of lymphocytes in the dermis.

Discussion.

Redness and slight oedema in the first patient were produced after an exposure which in normal subjects failed to produce any reaction, indicating that her minimal erythema threshold was lowered. The aggravation of the positive patch test after the exposure could be the result of a photoallergic, or rather a photodynamic mechanism. Spongiosis was already present in the simple test and cannot be used with certainty as evidence in favour of the photoallergic mechanism. An area patch tested with chlorpromazine and then exposed to light showed no eczematous features histologically. Redness was more intense than in ten controls in whom a positive reaction to patch testing followed by

light could be also produced with the 0·5% solution for intramuscular use, presumably because of the increased photosensitizing effect of chlorpromazine on skin in which the minimal erythema threshold was already lowered, in this case by promethazine. Thus strictly speaking, this was not a true cross photosensitivity between promethazine and chlorpromazine since it was not dependent on their structural formulae, but was merely the result of the capacity of both to produce photosensitization.

In Case 2, the area of patch test with sulphanilamide followed by exposure to light showed histologically an eczematous reaction, while that with promethazine was non-eczematous. One could speculate on a possible cross photosensitivity between sulphanilamide and the two phenothiazine derivatives ; a reduction in the latter two could produce a primary amine which might be structurally similar to that of sulphanilamide. It should be mentioned also that in my controls, solutions of chlorpromazine and promethazine which were exposed to sunlight and changed colour did not lose their photosensitizing property. Although I do not believe in such a possibility, I mention the frequently observed positive test to paraphenylendiamine in patients allergic to promethazine (Sidi *et al.*, 1955). Sulphanilamide, however, applied in both patch and scratch tests in controls did not produce any erythema after exposure. In this case the same mechanism as in Case 1 could be equally involved.

In the third patient, simple patch tests were negative, while those to promethazine and chlorpromazine followed by light showed redness and swelling. As the eruption followed the ingestion of promethazine, this test area was biopsied, with non-eczematous histological findings. In this case, with a distribution similar to the first two cases, a different (photodynamic) mechanism may be involved. Cross photosensitivity as the explanation of the positive reaction to chlorpromazine and light would be illogical, since there was no allergic sensitivity to promethazine.

In the fourth patient, the patch test to chlorpromazine was positive ; it was aggravated after exposure. There was, however, no light eruption. The patch test to promethazine also became positive after exposure to light. Histologically, only the former showed an eczematous reaction. Although the histologically eczematous reaction was aggravated by sunlight, photoallergy cannot be accepted as the explanation since there was no light eruption. We must then suppose that in this case the positive test was aggravated by the phototoxic mechanism. Considering only the positive tests to the two phenothiazine derivatives aggravated by sunlight, it cannot be said which was produced by the photoallergic and which by the phototoxic mechanism. A positive scratch test to sulphanilamide in a patient without a light eruption, however, is not aggravated by sunlight, neither is the same negative test in controls.

Reviewing previous " photoallergic " cases we see that both of those reported by S. Epstein (1957, 1960) had also positive reactions to a simple patch test

with phenergan. His first patient who was also tested with thorazine showed a positive reaction only after exposure to light ; it was explained as being due to cross photosensitivity. The first case of Schulz *et al.* (1956) had also a positive reaction to a plain patch test with megaphen, i.e. chlorpromazine. In their second case, which the authors thought it justifiable to include in this group because the minimal erythema threshold was lowered, a simple patch test was negative while after light exposure it became positive. In the remaining three cases also with light eruptions, skin changes were regarded as being due to the photodynamic effect of drug. H. J. Epstein *et al.* (1957) found among seventy-two persons who were taking chlorpromazine nine with an exaggerated response to the " B " carbon arc exposure ; two patients developed increased reactions while not taking the drug. They commented that it appeared that at least a small percentage of patients treated with chlorpromazine would become abnormally sensitive to certain wavelengths in the solar spectrum.

Patients who developed photoallergic eczema after using sulphanilamide ointment (Burckhardt, 1948), an oral antidiabetic drug (Burckhardt, 1957a) and a " blankophore " (Burckhardt, 1957b), had negative reactions to simple patch tests which became positive after exposure to light. These could be accepted as photoallergic. In another of my patients who developed a light eruption after the use of sulphanilamide the findings were similar. A simple scratch test, however, was positive. It is known that in simple contact sensitivity to sulphanilamide, as well as photosensitivity, patch testing gives erratic results (Peterkin, 1945), which might partly account for some negative findings. The term " photoallergy " could be used with certainty only for those cases in which patch tests (and scratch tests with sulphanilamide) were negative, while patch tests followed by light slowed histologically an eczematous reaction. We must accept that " photoallergy " can be associated with plain contact allergy. It is, however, impossible to prove the former histologically or clinically, since in both photoallergic and photodynamic effects the clinical picture is the same, except when it is eczematous. I also think that the minimal erythema threshold is lowered in both mechanisms for a certain length of time, varying from case to case ; otherwise I do not see how such erythema could be elicited after a casual exposure. Summarizing, it seems to me that most light eruptions due to drugs are due to the photodynamic mechanism, with a negative reaction to a simple patch test but a positive test after its exposure to light, showing no eczematous reaction, in an eruption localized on the exposed parts and conditioned by sunlight. It is independent of but can appear in association with simple contact sensitivity. The following comments on the subject of photoallergy may also be applied to photodynamism : " The tests with light alone produce an increased erythema and not an eczematous reaction ", or " after the use of the drug has been discontinued the florid sensitivity usually disappears within a few days or weeks " (Ippen, 1960). " Sunlight alone has

ceased to be an aggravating factor" (Epstein, 1960). The term "phototoxic" should be restricted to reactions to the same drugs which can be produced in all subjects. The number of patients showing light eruptions due to these drugs is surprisingly small considering their photosensitizing properties and wide use. It may therefore be justifiable to make a distinction between phototoxic and photodynamic properties. A photodynamic reaction is by its nature very similar to a photoallergic and in both the blood vessels probably react abnormally, but there is no eczematous reaction.

If, however, one accepts that an eczematous reaction to a patch test followed by exposure to light is not a prerequisite for the diagnosis of photoallergy, light eruptions could then be regarded as photoallergic, photosensitivity disappearing sooner or later. If such is the case, the specificity ascribed above to photodynamic action should go to photoallergy ; photodynamic action and photoxicity become synonymous.

No definite answer can yet be given. More experimental study is needed especially of cases photosensitive to sulphonamides, since there is no epidermal phototoxic effect with that drug. The possibilities mentioned above may also be considered.

Summary.

Three cases of light eruptions due to drugs are reported and the experimental findings are given. The mechanism involved in their production is discussed.

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CUTANEOUS VASOCONSTRICTORS, PRIMARY PIGMENTATION AND THE GREY-BLUE REACTION.

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This paper sets out to examine three questions :

(i) The assertion that cutaneous vasoconstriction can be correlated to a large extent with the specific chemical structure of the drug causing it, and that a considerable vasoconstrictor effect is found in the skin when at least one free —OH group is present on the phenyl ring of homologues of adrenaline. This has been stated in a paper by Stoughton *et al.* (1960).

(ii) The opinion that three factors are known to influence primary (immediate or direct) pigmentation in a susceptible subject, viz. the angle of incidence of the rays (following the cosine law), simultaneous infra-red irradiation and pressure anaemia. No other factors elicited comment in the thorough survey by Kimmig and Wiskemann (1959).

(iii) The demonstration that high energy long-wave ultraviolet rays may sometimes produce a grey-blue colour in the skin, held by Rottier and van der Leun (1960) to be associated with arteriolar paralysis and refractoriness of the arterioles to adrenaline.

Though seemingly dissimilar, these three topics link together the skin circulation with skin colour and ultraviolet radiation—hence their mutual relevance in the present study.

Amine Vasoconstrictors.

The existence of a *p*-hydroxyphenyl structure in a group of adrenaline-like vasodilators seems to upset proposition (i) above. Two of these sympatholytics and four sympathomimetic amines, all having *p*-hydroxyphenyl groups, were therefore investigated on the skin.

To avoid recrimination for necrosis, all injections of the undermentioned drugs were made intradermally in the flexor surfaces of the author's forearms in one minim (0·06 ml.) doses with serial dilutions by powers of 10. Only the salts of the amine bases were used. The sympathomimetics were tyramine hydrochloride (Light and Co.), 10^{0}–10^{-6} ; veritol sulphate (Knoll A–G), 10^{0}–10^{-6} ; paredrine hydrobromide (SKF Laboratories), 10^{0}–10^{-6} ; suprifen hydrochloride (Hoechst) 10^{0}–10^{-6}. The vasodilators were vasculat sulphate (Boehringer), 5×10^{0}–5×10^{-7} and duvadilan hydrochloride (N.V. Philips-Roxane, Amsterdam), 10^{-1}–10^{-6}, being respectively, 1-(*p*-hydroxyphenyl) 1-hydroxy-2N-butylaminoethane, and 1-(*p*-hydroxyphenyl)

1-hydroxy 2-(1-methyl-2-phenoxyethylamino) propane. Controls with normal saline and adrenaline hydrochloride 2×10^{-4} were used throughout.

With the four sympathomimetics, strengths of 10^{0}–10^{-6} gave a central red lump with a contiguous flare, and gradually tended to show pilomotion, particularly on light touch in the red area. As the lump flattened, some pallor with increasing pilomotion tended to appear like a moat between the lump and the flare, till after 30–60 minutes the spots resembled the earlier appearances of the same drug in weaker strengths, and became progressively paler throughout. The reaction was over in 1–2 hours. With concentrations of 10^{-2}–10^{-3} pallor and pilomotion were usual but lasted only between 30 60 minutes. Between 10^{-4}–10^{-6} strength solutions nothing or a slight but transient blanching was seen, passing in 15 minutes as a rule. Compression of the upper arm to 40 mm. Hg overcame all vasoconstriction readily except that of the adrenaline, whose effects lasted hours after the other amines had stopped working.

The two sympatholytics, both *p*-hydroxyphenylalkylamines with substituents on the amino nitrogen, were without much effect on the skin circulation. Duvadilan produced red spots, with a little of what Lewis might have called " balancing anaemia " about them, all over after $1\frac{1}{2}$ hours. Vasculat injections caused a trivial local upset, lasting less than half an hour, but no conspicuous anaemia or hyperaemia. None of the amines caused itching.

At times, a central red knob with a surrounding moat of pallor was noted with 10^{-3} solutions of adrenaline. This pallor could not withstand 70 mm. Hg pressure on the venous return. Subsiding central congestion was also heralded by pilomotion.

Polypeptide Vasoconstriction.

Somewhere, polypeptide vascular regulation and vascular allergic reactions must undoubtedly overlap, but while local blanching occurs one still remains within the domain of physiology. These blanching reactions are a little different from the amine effects noted above, but they were investigated in the same way. The findings presented here relate both to the preceding and succeeding portions of this paper.

Hypertensin II (Hypertensin Ciba), 10^{-1}-10^{-6}, showed in the two highest strengths a typical anaemic " moat " appearing between the central red knob and peripheral flare, and the pale area slowly ate up the central lump and the flare with some suggestion of pseudopod formation. " Moat blanching " as described here is indistinguishable from " delayed pallor ", thought by Lobitz and Campbell (1953) to be a characteristic reaction of atopic subjects to acetylcholine injections. The pallor from hypertensin spread rather slowly from the injection site, and the final size attained by the pale area was smaller with declining concentration. There was less pilomotion, flare or pseudopod formation. Injections of 10^{-3} and under were pale from the start, and all pallor was gone in one hour from the weaker spots.

Certain pituitary hormones were similarly tested at fixed dilution. Vasopressin (Parke Davis, 20 units/ml.) showed the pattern of slowly spreading " moat blanching ", with itch, flare, whealing etc. Oxytocin (Parke Davis, 10 units/ml.) showed a considerably delayed pallor developing from a slowly spreading and flattening wheal. There was a mild flare and no itch. ACTH (Armour, aqueous, 40 units/ml.) showed wheal whitening with extending pallor in flat pseudopods, in addition to flare and itch. TSH (thyrotropic hormone, Thytropar Armour, 5 units/ml.) showed a tension wheal and flare with no residual pallor.

Nervous and Vasomotor Effects on Primary Pigmentation.

In this group of experiments, adult Bantu male subjects were used, several tests of each type being performed and compared. It has been repeatedly confirmed since the work of Kooij and Scott (1954) that the Bantu exhibits primary pigmentation very readily on exposure of a normally covered part such as the back to direct sunlight for ten to thirty minutes.

During our study of primary pigmentation, we were privileged to have Dr. I. W. Whimster as a guest in our department, and following his suggestion, we jointly tested the effects of nervous influences on primary pigmentation.

It was found in these experiments that the nervous influences tested were without effect, but that even moderate changes in the circulation exerted important effects on the rate of direct pigmentation. Five groups of results were obtained in collaboration with Whimster. (i) Intradermal lidocaine 2% and procaine 2% injected as local anaesthetics failed to affect primary pigmentary responses. (ii) Marked changes in primary pigmentation were noted with local anaesthetics mixed with adrenaline (1 : 50,000). (iii) With procaine-adrenaline injected into a specimen of freshly excised Bantu skin, no pigmentary alteration whatsoever was observed after one hour's exposure to sun, the specimen being kept moist with normal saline solution. (iv) No alteration in primary pigmentation was seen in a Bantu subject in the pseudosegment of a broad but interrupted pseudosegmental naevus comedonicus where an undefined nervous influence might have been at work. (v) An attempt was made to test primary pigmentation in the hypopigmented patches of a maculoanaesthetic leper. The patient was unfortunately one of the few Bantu who failed to show primary pigmentation after half an hour, but Kooij has since supplied us with the following unpublished observations made in several lepers. He found that the pale anaesthetic patches show undoubted primary pigmentation in proportion to their pigment content and that it is possible to darken such patches artificially past the normal depth of skin colour with methoxypsoralen paint.

It is therefore likely that neural influences have little, if any, direct effect on primary pigmentation in man. The results (ii) and (iii) above furthermore made it probable that adrenaline affects primary pigmentation by its vasomotor action and not by a direct effect on the pigmentary behaviour of cells.

The action of vasomotor drugs on primary pigmentation was therefore studied and extended to a wider range of compounds. From these investigations, it was concluded that arteriolar flares accelerated primary pigmentation, vasoconstriction retarded it, and white or red wheals exerted a variable but sometimes trivial effect on primary pigmentation.

The experimental findings were as follows. (i) Excised skin shows no primary pigmentation whatever in the time normally taken for this to appear *in vivo* (ii) Primary pigmentation *in vivo* is slightly slower in areas where the circulation is less,

e.g. around follicles, aided sometimes by piloerection, and in areas of slight postural traction on the skin. (iii) Areas of immediate, persistent and absolute anaemia around the site of an adrenaline injection (1 : 20,000) fail to show primary pigmentation. (iv) Areas along lymphatic drainage channels of such an adrenaline injection site may show pale streamers where the pigmentation is delayed in the first five to fifteen minutes, but with irradiation of thirty minutes or more these lymphatic pseudopods become obliterated as they darken with the surroundings. (v) Where vasoconstriction is delayed or mild, as with 0·5% mecholyl chloride or oxytocin 10 units/ml. intradermally, an inhibition of primary pigmentation is seen only occasionally. (vi) The three drugs tested which most regularly caused central delayed primary pigmentation on intradermal injection, with pale streamer-like lymphatic pseudopods, were adrenaline hydrochloride 1 : 20,000, vasopressin 20 units/ml., and ACTH 40 units/ml. aqueous solution in this order of intensity of effect. With delayed vasoconstriction the effects of ACTH were sometimes doubtful. Where a central red knob resulted at the injection site, this spot did not show delayed pigmentation. I am indebted to Dr. F. P. Scott for suggesting the use of ACTH for these tests. (vii) Prompt marked arteriolar flares round the injection site were followed by a notably accelerated primary pigmentation. These were seen with ACTH, adrenaline, vasopressin and thyrotropic hormone in strengths stated above. It was apparent that a traumatic triple response might exert mild effects on primary pigmentation, but a prompt and intense flaring property of the injected substance was decisive. A central red knob at the injection site of a vasoconstrictor showed less enhancement of primary pigmentation than the surrounding flare. (viii) Vasodilators which caused wheal formation had little effect in hastening primary pigmentation, with the occasional exception of priscol. Drugs tested were 2% histamine acid phosphate jelly and 10% priscol (Ciba) solution by iontophoresis and 5% trafuril (Ciba) cream by inunction. (ix) In a few instances, mild flare hyperpigmentation was noted in the covered control site. This was seen after irradiation in the covered half of areas in which adrenaline and mecholyl had been introduced by iontophoresis, outside the area of placement of the positive plate, in the region where the flare occurs. It was also once seen in a flare after an intradermal injection of 0·5 ml. adrenaline 1 : 30,000, where half the injection wheal was covered during exposure to sunshine. Heat may therefore have contributed to the hyperaemic darkening. (x) 5-hydroxytryptamine (Antemovis Vister, 0·25%) intradermally was without effect on primary pigmentation. (xi) Mecholyl chloride (Merck Sharp and Dohme, 0·5%) by injection and iontophoresis showed extremely variable or patchy pallor and flare reactions of the type that resulted in inconstant pigmentary effects. Once only a curious pigmentary reticulum was produced round an irradiated injection site with this drug. (xii) TSH intradermally, but for the pigment enhancement in the flare noted above, was without influence on primary pigmentation.

The following precautions assisted in interpreting the results. All flares or erythema in dark skins were judged in strong sunlight. Observations were made on the test subjects at least once in five minutes. Allowance was made for optical illusions where judging colour in adjoining pale and dark areas. With intradermal injections of larger volumes particularly, traumatic haemorrhage was differentiated carefully from primary pigmentation.

The Grey-blue Reaction.

While experimenting with the vasoconstrictors, some observations appeared to elucidate the vexing reaction referred to in proposition (iii) of the introduction to this paper. Though unconfirmed so far, the validity of the observations of Rottier and Van der Leun is accepted here without question, but their interpretations present difficulties refractory to physiological integration. First,

they describe a discoloration which, though given no such name, could surely on the evidence be nothing more than a patch of cyanosis due to stasis in the dilated subpapillary venous plexus. A deeper plexus is hardly likely to be responsible. Second, they mention a transitory intensification of this blue colour after pricking in adrenaline. Their explanation of dilatation of an arteriolar plexus with insensitivity to adrenaline can hardly expect to find general acceptance as the cause of this colour reaction. Any slight brownish primary pigmentation also possibly seen by them makes little difference to the main problem of interpretation.

Though differently produced, exactly the same class of reaction was studied by us in the following circumstances. Subsiding flares were seen to pass through a nondescript phase when the arterioles were presumably not widely open any more, but the vessels of the venous plexus probably remained widened. It was found best to view such a fading flare indoors under fluorescent tube lights. The slight but curious changes of texture and colour seen in strong sunlight are hard to put into words. Under tube lights the last vestiges of the flare appear a characteristic grey-blue, and look like fading bruises or thin smears of motor grease on the skin. On pricking adrenaline into such an area, it is temporarily asphyxiated by further vasoconstriction, and with a slight rise in venous pressure the venous plexus is forced open and the static blood becomes even bluer from further desaturation at the site of the puncture where the hypoxia is greater. (Rottier and van der Leun's experiments were performed on the arm where this might readily have occurred.) Alternatively, the adrenaline can induce a central red reaction which will become intensely cyanotic, surrounded by a zone of vasoconstriction which ensures stasis.

The venous plexus need not of course be opened by preceding arteriolar flushing, since exactly the same sequence can be studied by placing a compression cuff on the arm, tight enough to force the venous plexus open, but not too much to counteract the extra asphyxia from the adrenaline puncture. I believe also that some slightly congested naevi flammei can acquire a grey-blue colour in rather the same way. An analogous phenomenon in fading urticarial patches is more frequently seen.

It is therefore suggested that the grey-blue reaction represents a cyanotic stasis in the dilated but not telangiectatic or cavernous subpapillary venous plexus. It can arise in several ways, of which high doses of long-wave ultraviolet light may at times be one.

Summary.

Cutaneous vasoconstrictor action of a certain group of sympathomimetic amines (the *p*-hydroxyphenylalkylamines) was absent in compounds with large substituents on the amino nitrogen. With amine and polypeptide vasoconstrictors, red pilomotor wheal and delayed blanching reactions were seen with

higher concentrations of the drugs. When the maximum pure vasoconstrictor dose was exceeded, red wheals resulted, and vasoconstriction then set in slowly during the regressive phase of drug action.

Primary pigmentation in the skin was greatly altered by local circulatory changes of all degrees, the results depending on the drugs used for this purpose, but nervous stimuli were evidently without direct effects. It appeared that primary pigmentation could be induced by heat combined with arteriolar flushing alone.

Some sources of grey-blue vascular tints in the skin were considered, in an attempt to find an acceptable explanation for the colour which is said sometimes to occur after heavy long-wave ultraviolet irradiation.

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SKIN PIGMENTATION CAUSED BY EPIDERMAL STRIPPING WITH ADHESIVE TAPE.

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This report describes a darkening of the skin which could readily be elicited by epidermal stripping in the dark-skinned Bantu. The pigmentary response could be altered by varying the number of times the strippings were performed, and appeared to follow damage at the level of the outer Malpighian layers. It has features in common with post-erythemal sun tanning and with pigmentation following alpha particle radiation from thorium X or polonium (Po^{210}).

Investigation.

The technique was based on the celebrated report by Pinkus (1952), in which he described the stripping procedure as a stimulus for epidermal mitosis. Areas of normal skin unexposed to light on the upper back of 3 adult Bantu males were stripped by repeated application and removal of plastic adhesive tape bands 1 inch by 4. Punch biopsies were done without disinfecting the skin. The sections were fixed in picroformol embedded in paraffin and stained with Lillie–Mayer haematoxylin; melanin staining was avoided so as to leave the pigment nearer its natural colour.

Subject 1.—Dark skinned. Five areas stripped—5, 10, 15, 20 and 25 times. Observation time 6 weeks. No biopsy.

Subject 2.—Dark skinned. Six areas stripped—5, 10, 15, 20, 23 and 25 times. Observation time $3\frac{1}{2}$ weeks. Biopsies from control site and at 24 hours, 72 hours (2 specimens) and 10 days from areas stripped 25 times.

Subject 3.—Pale skinned. One area stripped 25 times. Observation time 3 weeks. Biopsies from control site, and from stripped area immediately after stripping and at 48 hours. Part of the stripped area was briefly wiped with 10% aqueous zephiran immediately after stripping, and this " burnt " area was biopsied 48 hours after.

Results.

Twenty-five strippings produced a diffusely moist, shiny pink and slightly painful surface. After one to two days the area showed a sharply marginated, smooth, deeply placed fixed pigmentation resembling direct pigmentation induced by long-wave ultraviolet light. In Subject 3 this change was less marked. Once darkening set in, no pinkness was detectable and all surface moisture had disappeared. During the first week the colour grew progressively darker, a change which was confirmed photometrically by a method described elsewhere (Findlay, 1960). It seemed as if the pigment was becoming more superficial, since a wrinkled surface scale gradually formed, which was as highly pigmented as can be seen in pellagra. In the middle of the first week after stripping, the

tripped area was surrounded by a hypopigmented border. By the end of the second week, the dry black puckered scale had largely cracked and peeled off. The underlying epidermis was then seen in Subjects 1 and 2 to be smooth and diffusely blackened. In Subject 3 the epidermis underneath was paler than normal. In the remaining periods of observation the colour gradually approached the normal in all cases but the colour differences remained conspicuous notwithstanding.

Histologically, the "resting" control specimens showed the usual heavy concentration of melanin in the basal layer, both in granular and apparently amorphous forms ("ultramelanin", Breyer (1938); "caramel", Findlay (1961*a*); "premelanin", other authors). Suprabasally there were mainly discrete pigment granules in the epidermal cells with no thick amorphous pigment matrix. After stripping, the outer Malpighian layers condensed to form a parakerototic stratum corneum while all epidermal layers were regenerated afresh by the surviving cells below this by the tenth day.

The following changes in pigment were noted :

(i) A clearing of pigment from the basal layer was evident within the first three days. The changes which take place are, to use Hermann Pinkus' phrase, "wide open to personal interpretation". The interpretation offered here is a triple one—a distribution of the basal cell pigment among the daughter cells in the regenerating layers, causing them to occupy a greater thickness of epidermis ; a blackening of the granules, larger numbers appearing jet black by comparison with the controls ; reduction in the amount of amorphous melanin, associated with blackening of cell structures such as tonofibrils, nuclear membrane, etc. This type of pigmentation was described as a normal feature of dermal melanoblasts (Findlay, 1953).

(ii) The appearance of numerous pigment granules in the parakeratotic cells, becoming more conspicuous as the layer dried out. They appeared blacker than in the control, but it was impossible to judge if they were more plentiful. There was nothing to suggest that the granules were of larger, paler chromatophore type or extra-cellular in position.

(iii) Melanoblast dendrites started to fill with black pigment granules from the third day and were marked at the tenth day (Subject 2). This wave of active melanogenesis therefore came later than the changes described in (i) and (ii) above. Melanogenesis was doubtless stimulated in Subjects 1 and 2, and depressed in 3, to account for the pigment differences after separation of the parakeratotic scale.

Epidermal necrosis from zephiran (Subject 3) was associated with intense melanin pigmentation of the slough. Histologically, the damaged epidermis at 48 hours showed no change in the numbers of cells or position of the pigment. The pigment was still present in the basal cells, but much blacker and more condensed around the fibrils and nuclear membrane. This change alone was

considered to account for the extreme clinical darkening, all the cells having been killed *in situ*. Melanoblasts must have been destroyed as well, since repigmentation after separation of the eschar was follicular at the start.

Pigment changes from stripping less than 25 times.—No stripping was quite even, nor were all reels of tape equally sticky. When stripping upwards of ten times, areas of moist epidermis were exposed to a varying extent. With fewer than ten strippings, only a matt grey surface resulted from disruption of the stratum corneum. No moist areas were exposed and no pigment alteration seen. Between ten and twenty-five strippings, the results were evenly graded. It was found that the more the stripping the earlier the darkening, the more massive and persistent the ensuing pigmented scaling, and probably the more intense the pigmentation persisting beneath the scaling layer. Thus in Subject 2, the area stripped ten times showed mild pigmentation in a smooth skin visible on the sixth day and almost faded by the thirteenth day. This would correspond to melanoblast stimulation only. In Subject 3, the darkening of stripped and killed epidermis showed pigment darkening only. Intermediate strippings would then illustrate the combination of pigmentary shifts, changes of state and darkening, backed up to a variable extent by renewed melanogenesis.

Discussion.

Stripping or abrasive pigmentation differs from other types mainly in the banality of the stimulus and the fact that the response is marked only in dark-skinned subjects. Some initial drying out of the superficial Malpighian layers appears to be essential for the reaction to occur and then the results are remarkably like those of sunburn and damage from alpha particles. With these types of radiation one also meets with early changes confined to the outer Malpighian layer followed by delayed pigmentation, peeling of the tan and hyper- or hypopigmentation of the underlying epidermis (Hamperl *et al.*, 1939 ; Becker *et al.*, 1952 ; Witten *et al.*, 1957 ; Staricco, 1957).

Interpretations presented in this paper for the colour changes rest on two fundamentals—first, the presence of melanin carried inside the epidermal cell, a proposition convincingly argued by Staricco and Pinkus (1957) and second, the active influence of the carrier cell in altering the colour and form of the pigment, which has mainly been investigated as direct pigmentation or the Meirowsky phenomenon (Findlay, 1961*a*).

Regarding the effects of the carrier cell on the colour and form of the pigment, some type of radiation is often considered necessary for changes to occur. However, it is likely that darkening could result physiologically in at least three other ways. First, active hyperaemia can increase pigmentation (Findlay, 1961*b*). Second, during cell shifts and impending mitosis the epidermis becomes actively aerobic (Bullough and Johnson, 1951). This is the cell state which

predominates after stripping, and could possibly lead to oxidative darkening of melanin. Thirdly, there is a variable ceiling for melanogenesis imposed by the epidermis. This phenomenon, discovered by Rothman and Magnin (1957), could conceivably be altered by a banal stimulus such as stripping.

Summary.

Mild denudation of a dark skin was shown to induce pigmentation comparable with that of sunburn. The effects are not considered to be due to stimulation of melanoblasts alone. The epidermis is believed to play an active part in altering the melanin contained within its cells.

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OBITUARY.

Ivan Henry McCaw.

Dr. Ivan McCaw who died on the 17 March 1961 in Belfast at the age of 64 was the son of Dr. John McCaw, one of the first specialists in Belfast in diseases of children. He was educated first at the Royal Belfast Academical Institution and in 1914 at the end of his school days, he entered the Queen's University, Belfast, as a medical student. In 1915 he was commissioned in the Royal Irish Rifles and in 1917 he was severely wounded in the Battle of Messines. Later he resumed his medical studies at the Queen's University, graduating with honours in 1922. Having in due course

decided to make dermatology his career he studied first in Edinburgh, then in Vienna and finally he became a clinical assistant to the late Dr. H. W. Barber at Guy's Hospital. On his return to Belfast he was appointed Physician to new departments of dermatology in the Royal Victoria Hospital and Royal Belfast Hospital for Children, these being the first posts of the kind to be created in Northern Ireland.

He never appeared to think of himself as an outstanding figure in dermatology and he chose to write very little, but he was a first class clinician and he was always in the front rank of British dermatologists, a fact which was duly recognized when he was made President of the British Association of Dermatology for 1948. In

addition he had constructive vision and the gift of leadership, qualities which were of immense value in building a dermatological service for Northern Ireland. Under McCaw's reign the dermatological work of Northern Ireland has been closely and most beneficially integrated. Its centre today is a splendid new department in the Royal Victoria Hospital and this has been staffed by four out of five consultants who have formed the country's dermatological team, the duties of the fifth being too distant to allow him to work also in Belfast.

McCaw was a very well known figure outside as well as within the medical profession. In 1951 he was President of the Queen's University Services Club, an honour which no doubt reflects in some degree the regard and affection in which he was held by his fellow countrymen. He was splendid company, warmly interested in people and in all kinds of affairs, utterly unselfish, always gentle and abundantly endowed with a highly entertaining variety of humour. He was fond of golf and within the limits imposed on him by a badly disabled right arm he was about as good a golfer as it was possible to be, an agreeable opponent always but formidable. He was Captain at one time of the world famous Royal County Down Golf Club.

Though died relatively young he lived to see the outcome of his life work, a solid and enduring contribution to medical progress in the country he loved. He will ever be remembered with admiration and affection by his colleagues and friends.

G. B. D.

R. H. writes.—Dermatology in Northern Ireland has suffered a great loss with the recent death of Ivan McCaw. From 1926, he carried the load in this area single handed until he accepted me as is first assistant in 1938. He developed a first-class dermatological service for Ulster and, with his encouragement, further dermatologists were trained and appointed so that at his death skin clinics were being carried on in fifteen Ulster hospitals by five consultant dermatologists. He never spared himself in carrying out his duties, and his vast clinical experience and excellent judgment were always much sought by those of us who had the privilege of working with him. We mourn the death of a revered and beloved colleague and his memory will be for ever green as the real founder of modern dermatology in this area.

J. M. B. writes : the late Ivan McCaw was outstanding in several enviable ways—he was kind, considerate, gentle, patient and loyal to a degree seldom found in one man. In fifteen years of dermatology, I shared four outpatient clinics each week with him : indeed, for more than half of this work we shared the same room. During all this time I never saw him ruffled or annoyed. Yet in his last five years, ever since the tragic motor-car accident in which his brother-in-law was killed, Dr. McCaw had little good health. It seemed that from that time on he had one illness after another, culminating in the painful and distressing one from which he died.

His loyalty was outstanding—he was loyal to his country, his specialty, his hospitals and his family and he lived his entire life for these things. He would never let a colleague down and his patients adored him. During his final illness he showed a degree of bravery which could hardly be matched. He started dermatology alone in Northern Ireland : he leaves behind a service in which twenty-one people are involved full time. He will not be forgotten.

CURRENT LITERATURE

GRISEOFULVIN. R. Degos, E. Rivalier and P. Lefort. (1960) *Ann. Derm. Syph., Paris*, **87**, 121.

The authors carefully survey the world literature on griseofulvin and give their own experiences at the St. Louis Hospital which coincided with those of other dermatologists. No case has been epilated with x-rays since March, 1959. It is striking that favus, which used to be the most resistant fungus infection of the scalp, responds more readily than animal microsporosis. The authors claim to cure ringworm of the toe nails in five to seven months. F. F. H.

THE MODE OF ACTION OF GRISEOFULVIN ON DERMATOPHYTES (INHIBITION OF KERATOLYTIC POWER). P. Rimbaud, J. A. Rioux and J. M. Bastide. (1960) *Ann. Derm. Syph., Paris*, **87**, 145.

The authors exposed a normal hair from a boy with favus who had been treated with griseofulvin for three months to a culture of *Ctenomyces mentagrophytes*. The hairs resisted invasion by the fungus which attacked normal control hairs. After a period the resistance of the griseofulvin hairs seems to diminish. From the above the authors conclude that the action of this agent is an inhibition of the keratolytic activity of the fungus. F. F. H.

PSEUDO SCLERODERMATOUS LESIONS IN RHEUMATISM. S. Jablonska and B. Bubnow. (1960) *Ann. Derm. Syph., Paris*, **87**, 241.

Scleroderma can co-exist with chronic polyarthritis, usually developing after the rheumatic manifestations. Chronic polyarthritis and rheumatism of the soft tissues can however give rise to pseudosclerodermatous lesions. Differential diagnosis depends on the clinical picture, radiological signs, histology and the estimation of sensory chronaxy. Diagnosis is important for its bearing on prognosis. The authors present the description of three patients in illustration of the above. F. F. H.

CUTANEOUS GANGRENE IN INFANTS. Nguyen-Van-ut. (1960) *Ann. Derm. Syph., Paris*, **87**, 279.

Cutaneous gangrene affecting children of from two to eight weeks is common in Viet-Nam. A clinical description is given based on thirty cases. The prognosis is grave (33% mortality). The causal agent in half the cases was a staphylococcus. F. F. H.

MONGOLIAN OLIGOPHRENIA AND CONGENITAL ECTODERMOSES. Lionel Rapaport. (1960) *Ann. Derm. Syph., Paris*, **87**, 263.

A clinical and statistical study of mongolism shows the frequency of associated ectodermal anomalies—hyperkeratosis, hypopigmentation of the hair and lens opacities, and the rarity of caries. New American statistics show the parallelism between the geographical distribution of mongolism and the content of fluorine in the drinking water. F. F. H.

TUBEROUS XANTHOMATA APPEARING THIRTEEN YEARS AFTER ARTERIAL HYPERTENSION AND CORONARY ACCIDENTS. B. Duperrat and J. L. Beaumont. (1960) *Ann. Derm. Syph., Paris*, **87**, 258.

The authors describe a patient who underwent a period of starvation from 1940–1945 and then one of excessive intake of food. He developed malignant hypertension and various vascular accidents with increasing cholesterolaemia and xanthoma tuberosum. Biological tests showed that the condition was one of essential hyperlipaemia and underlined the importance of an absolutely fat free diet. F. F. H.

NAIL CHANGES IN THE COURSE OF FOLLICULAR LICHEN PLANUS. P. de Graciansky, S. Boulle, I. Zucman and Mme M. Boulle. (1960) *Ann. Derm. Syph., Paris*, **87**, 361.

The authors describe a patient with nail changes, chiefly onychorrhexis and associated minimal follicular lichen planus. They review the various nail changes that have been reported with lichen planus and in particular onychorrhexis and ungual atrophy and onycholysis. They believe for

various reasons including capillaroscopic examination of their patient, that onychorrhexis is a direct consequence of a local lichen planus lesion and not just a trophic change; furthermore there are features of the onychorrhexis which distinguish it from that found in eczema, psoriasis, etc., so that it has a diagnostic value of its own. F. F. H.

ULCERATED ATROPHIC LICHEN PLANUS WITH MALIGNANT DEGENERATION. L. H. Jansen and F. B. G. Groothuis. (1960) *Ann, Derm. Syph., Paris*, **87**, 371.

A woman who had had ulcerated atrophic lichen planus for 34 years developed an epithelioma of the left foot and later one on the right elbow. F. F. H.

HEREDITARY ONYCHO-ARTHRO-OSTEODYSPLASIA (ONYCHARTHROSIS OF TOURAINE). R. Lacroux, J. Philippon and J. P. Poirer. (1960) *Ann. Derm. Syph., Paris*, **87**, 382.

This condition, known in England as Turner's syndrome despite prior descriptions by other authors, may present nail dystrophies and bony abnormalities particularly in the region of the knees and the elbows and other joints. The authors report a boy aged 19 who showed a wide variety of these changes. In three generations, five out of eight persons were affected, the condition being inherited as a dominant. F. F. H.

A NEW EPIDEMIC DERMATOSIS IN INFANTS. C. Cam. (1960) *Ann. Derm. Syph., Paris*, **87**, 393.

Since the summer of 1956, the author has seen more than 500 children suffering from what appears to be a hitherto undescribed skin disease. The condition starts with diarrhoea, fever, vomiting and papular lesions. These latter enlarge in a serpiginous fashion and form reddish plaques or rings especially on the extensor surfaces of the limbs but also on the trunk. The children lose weight and become debilitated, and a number die. The liver is always enlarged. Almost all the children were breast fed by mothers who had eaten seed corn treated with hexachlorobenzene. At the same period numerous cases of cutaneous porphyria of hepatic type were discovered in the same region. The livers of the mothers were also found to be enlarged and some showed porphobilinogenuria. Treatment consisted of terminating the breast feeding and general supporting therapy. The author believes the children's condition was due to some toxic body coming from the mother's milk. F. F. H.

COMPARATIVE STUDIES OF INDUSTRIAL DERMATOSES IN THE METAL INDUSTRY. S. Borelli and M. Manok. (1960) *Derm. Wschr.*, **141**, 613.

Over 6000 workers were investigated. In plant A where preventive measures were employed the occurrence of dermatitis was halved (3·5% as opposed to 7·4% in plant B where similar work was carried out without " prophylaxis "). Degreasing agents and solvents are a major factor in provoking dermatitis and prevention is difficult. The same applies for oil acne and folliculitis which occur not infrequently, and usually affect circumscribed areas. Tinea pedis was found in 12% of the working personnel of plant A and 17% of plant B (over 14% of the total). Wearing rubber boots is an important factor and it appears that the addition of a fungicidal substance to the specially constructed foot bath in plant A has reduced the incidence by about 5%. J. M.

ECTHYMA GANGRAENOSUM. K. H. Trimczek. (1960) *Derm. Wschr.*, **141**, 617.

After a survey of the literature one case is described in a 56-year-old man. There was no evidence of ulcerative colitis; the condition followed trauma at work and a dog bite. Antibiotics were useless. Deep excision and above all steroids promoted healing. The patient had to continue on a maintenance dose. J. M.

A CASE OF MYCOSIS FUNGOIDES WITH PARAPSORIASIS AND POIKILODERMA. K. Sipos and I. Deme. (1960) *Derm. Wschr.*, **141**, 669.

A male patient aged 47 developed after the premycotic stage typical widespread tumours of mycosis fungoides. They responded to X-ray therapy and nitrogen mustard injections and painting. At that time lesions of parapsoriasis en plaques occurred on the trunk. Eight years later (during which period the patient remained well) patches of poikiloderma atrophicans vasculare made their appearance on the trunk and extremities as well as tumours of mycosis fungoides. The author feels that the occurrence and particularly the sequence of these three conditions is unusual. J. M.

FISTULA CONGENITA PHARYNGO-CUTANEA. J. Tscheschmedjiev and S. Chlebarov. (1960) *Derm. Wschr.*, **142**, 764.

A young man complained about the appearance of a mucous discharge during meals at the site of a minute opening on the right side of his neck. A congenital fistula was present between the mesopharynx and the cervical skin and was probably connected with an ectopic mucous gland.
J. M.

TREATMENT OF ERYTHEMA ELEVATUM DIUTINUM WITH LEDERKYN. K. W. Kalkoff. (1960) *Derm. Wschr.*, **142**, 788.

Dramatic improvement in an extensive case affecting a 9-year-old girl is reported. The dosage was 2 tablets for 1 day then 1 daily with ½ tablet as maintenance dose. The author employed this long-acting sulphonamide in view of the fact that at one stage the lesions looked not unlike dermatitis herpetiformis and he conjectures a possible connection between these two conditions.
J. M.

JUVENILE MELANOMA OF THE CONJUNCTIVA. H. Gartmann and K. Thurm. (1960) *Derm. Wschr.*, **142**, 805.

A detailed clinical and histological account is given. This appears to be the first case involving the eye. Juvenile melanoma has so far only been described on the skin or tongue. J. M.

LUPUS ERYTHEMATOSUS AND PAROTITIS. J. Trapl and M. Sabatova. (1960) *Derm. Wschr.*, **142**, 817.

A male middle-aged patient with histologically confirmed L.E. of the face developed bilateral swellings of the parotid glands. Both conditions deteriorated after exposure to sun and improved on treatment with antimalarials and cortisone. The histology of the parotid tumour was similar to that of L.E. profundus. J. M.

ACUTE PYOCYANEUS INFECTIONS OF THE SKIN. P. Moeslein. (1960) *Derm. Wschr.*, **142**, 841.

A marasmic infant aged 10 months with multiple skin ulcers is considered to have suffered from ecthyma gangraenosum (e. cachecticorum). The author, after reviewing the literature since 1920, feels that this label should be reserved for ulcerative conditions caused only by *Ps. pyocyanea*. This child was gravely ill and the condition responded to streptomycin.
J. M.

BERYLLIUM, SELENIUM AND PHOTOSENSITIVITY. H. Jausion, A. Mazabraud and G. Lemoux. (1959) *Acta Allergol.*, **14**, 247.

No photodynamic or photosensitizing properties could be demonstrated in these substances.
H. T. H. W.

IN-VITRO FIXATION OF SKIN-SENSITIZING ANTIBODIES TO SKIN CELLS AND MESENCHYMAL TISSUE. Tage Samsøe-Jensen and Kristine Hauge-Kristensen. (1960) *Acta Allergol.*, **15**, 202.

Serum containing skin-sensitizing antibodies was incubated with untreated, frozen and heated skin, also with muscle fascia and peritoneal connective tissue. Prausnitz-Küstner reactions showed *in vitro* fixation of the antibodies to untreated and frozen skin but not to heated skin or mesenchymal tissue.
H. T. H. W.

CUTANEOUS PORPHYRIA IN TURKEY. R. Schmid. (1960) *New Engl. J. Med.*, **263**, 397.

During the last four years a large number of persons, both young and old, developed signs and symptoms found in porphyria. The urine was red and contained large amounts of porphyrins, as did the faeces. Bullae, loss of tissue, pigmentation and hypertrichosis were present on exposed areas, and the liver was often enlarged. There were no abdominal or neurological symptoms. The outbreak was attributed to eating wheat meant only for planting, which had been treated with the fungicide hexachlorobenzene. This is believed to be the first report of acquired toxic porphyria in man.
A. D. P.